(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 140 434**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **84201447.4**

(22) Date of filing: **09.10.84**

(51) Int. Cl.⁴: **A 61 K 9/06**
A 61 K 9/72

(30) Priority: **21.10.83 IT 2339683**

(43) Date of publication of application:
08.05.85 Bulletin 85/19

(84) Designated Contracting States:
AT BE CH DE FR GB LI NL SE

(71) Applicant: **PRODOTTI FORMENTI S.r.l.**
Via Correggio 43
I-20149 Milano(IT)

(72) Inventor: **Casadio, Silvano**
Via Tantardini 15
I-20136 Milano(IT)

(72) Inventor: **Casadio, Vittorio**
Corso Italia 45
I-20122 Milano(IT)

(74) Representative: **Appoloni, Romano et al,**
Ing. Barzanò & Zanardo S.p.A. Via Borgonuovo 10
I-20121 Milano(IT)

(54) Pharmaceutical composition with systemic anticholineesterasic, agonistic-cholinergic and antimuscarinic activity.

(57) The present invention relates to a pharmaceutical composition with systemic anticholinesterasic, agonisticcholinergic and antimuscarinic activity, characterized in that it contains a therapeutically active dose of a parasympathomimetic quaternary ammonium salt, and a nasal carrier suitable for the nasal administration of it.

EP 0 140 434 A2

Disclosure

Among the drugs of the autonomic nervous system, the parasympathomimetic drugs, and above all the anticholinesterasic and the antimuscarinic drugs, are important in the therapy of the illnesses of the gastroenteric apparatus characterized by spasm, gastric hypersecretion, hypermotility and in the therapy of atonies of the smooth muscle tissue of gastroenteric tract, of urinary vesica, and in the treatment of myasthenia gravis. Many of these parasympathomimetic drugs have the structure of quaternary ammonium salts (which will be denominated hereunder also as onium salts or compounds). Unfortunately, the bioavailability of onium compounds, administered by the oral way, is nearly always unsatisfactory, and however much lower than that consequent to the administration by the parenteral way.

This insufficient bioavailability of the onium salts under examination is evidenced by the large differences in LD_{50} observed as a function of the various administration ways (from literature references).

For the butylbromide of scopolamine the following LD_{50} values are e.g. reported for mice:

15,6 mg/kg by intravenous way
74 mg/kg by parenteral way
570 mg/kg by subcutaneous way
3.000 mg/kg by oral way.

Such values are, always for mice, respectively as follows, for prifinium bromide:

11 mg/kg by intravenous way
43 mg/kg by parenteral way
30 mg/kg by subcutaneous way.

330 mg/kg by oral way.

The large differences in absorption and bioavailability observed as a function of the different administration ways means, in the therapeutical practice, that oral dosages should be much higher than parenteral dosages. Neostigmine, e.g., is prescribed for parenteral administering in 0,5 mg-vials (on the average, 3 vials per day), whilst the lozenge dosage is 15 mg per lozenge, and the daily dosage may be as high as 20 lozenges.

Prifinium bromide dosage is 4 mg per vial, 25 mg per capsule, and 50 mg per suppository.

Thiemonium methylsulphate dosage is 4 mg per vial, 25 mg per lozenge, and 50 mg per suppository.

Emepronium bromide dosage is 50 mg per vial and 100 mg per lozenge.

The limited oral bioavailability of said onium salts is confirmed by the pharmacodynamic researches carried out on man, which have shown bioavailability rates by oral administration of the order of from 3 to 5% of those achieved by means of intravenous administration.

Among the causes which have been considered to be responsible for such large differences in bioavailability, the reduced penetration of onium salts through the gastrointestinal mucosa, with consequent inhibition to reach the smooth muscle cellular receptors, is one which has found experimental confirmation.

Onium salts are virtually insoluble in the lipoidal components of the membranes of the mucous cells of the gastrointestinal segment, and this is probably the most important barrier against the absorption of the same salts.

It must however be outlined that it is generally recognized that the absorption of ionized drugs by the intestine takes place in a reduced amount and in an unreliable way; this is particularly true for the drugs of the class of quaternary ammonium salts.

Finally, it is well known that the absorption through the gastrointestinal tract can be conditioned by the quantity and the nature of the food which is present inside the stomach, by the gastrointestinal motility, by the transit time, by the capability by the microbial flora to deactivate the active principle, and by the metabolizing connected with the first-pass effect.

Purpose of the present invention is to prepare novel pharmaceutical compositions of such drugs, which give therapeutical performances similar to those to be reached by the parenteral administration way, but which are cheaper and better acceptable by the patient.

In particular, according to the invention, the novel pharmaceutical compositions being searched for must produce a high bioavailability of the active principle and uniformity of hematic levels, properties which are absent in the compositions for oral use of the same active principles.

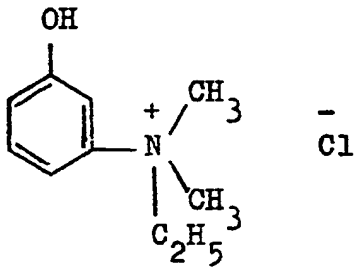
In order to achieving such purposes, the invention provides a pharmaceutical composition with systemic anticholinesterasic, agonistic-cholinergic and antimuscarinic activity, characterized in that it contains a therapeutically active dose of a parasympathomimetic quaternary ammonium salt, and a nasal carrier suitable to its administration by nasal way.

The structural formulae are described hereunder,

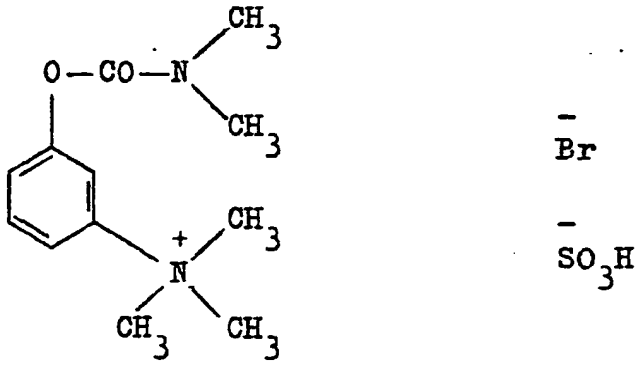
for exemplifying purposes, of parasympathomimetic quaternary ammonium salts, suitable to the purposes according to the present invention.

As regards compounds with prevailingly anticholinesterasic and agonistic-cholinergic activity, the following are mentioned:

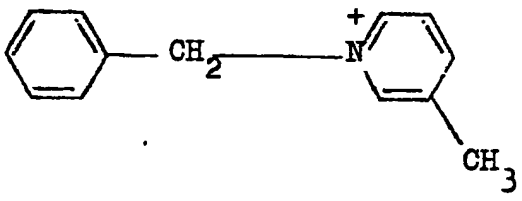
Edrophonium chloride



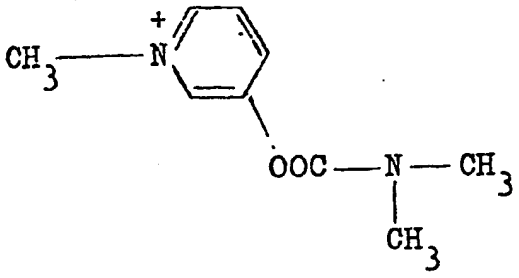
Neostigmine bromide and methylsulphate



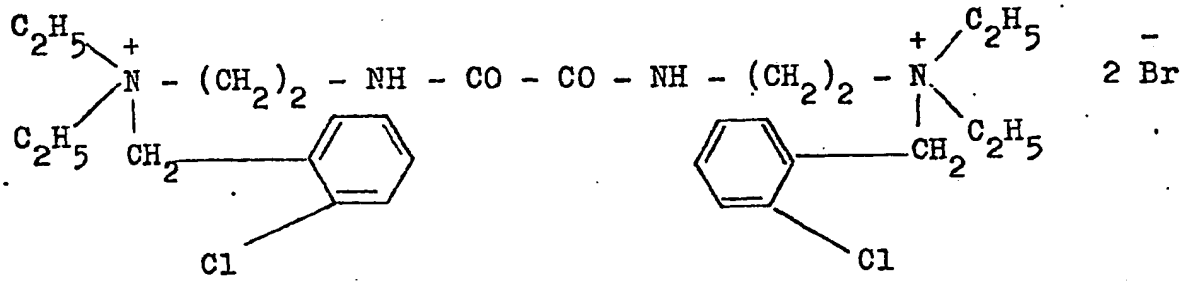
Benzpyrinium bromide



Pyridostigmine bromide



Ambenonium bromide



The parasympathomimetic onium salts with antimuscarinic action selected for use in the compositions according to the present invention comprise preferably:

Onium salts of esters of tropic acid

such as atropine methylbromide and methylnitrate, methscopolamine bromide and nitrate and scopolamine butylbromide.

Onium salts of esters of substituted acetic acids (disubstituted)

such as anisotropine methylbromide.

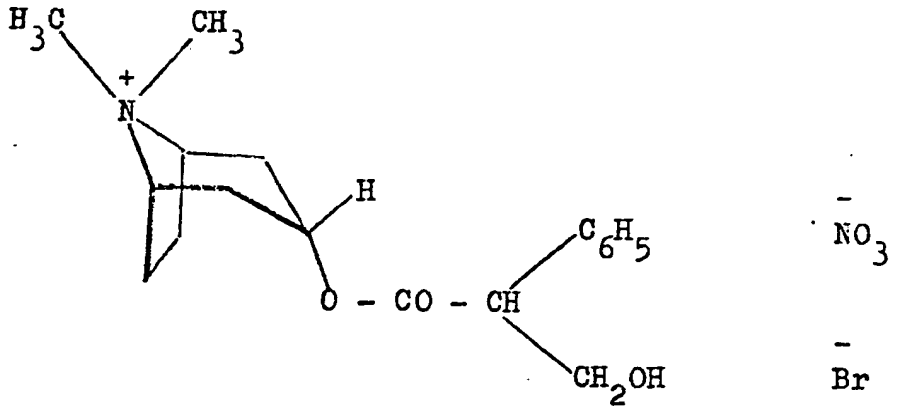
Onium salts of esters of benzilic acid

such as mepenzolate bromide, pypenzolate bromide, poldine methylsulphate, benzilonium bromide.

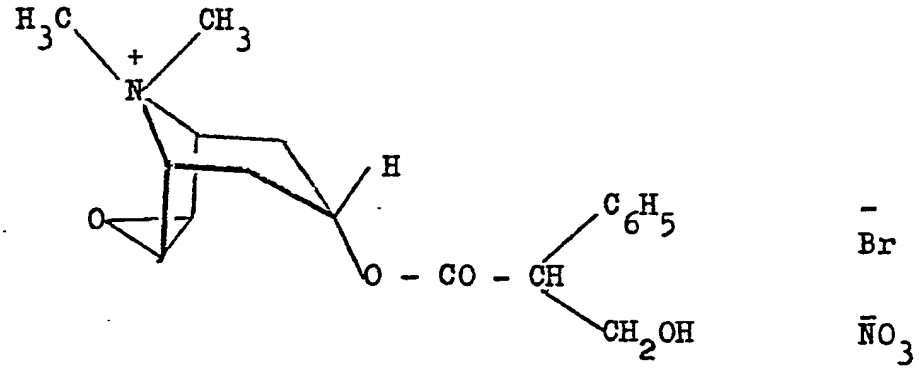
Onium salts of esters of phenylcyclohexylglycolic acid

such as oxyphenonium bromide.

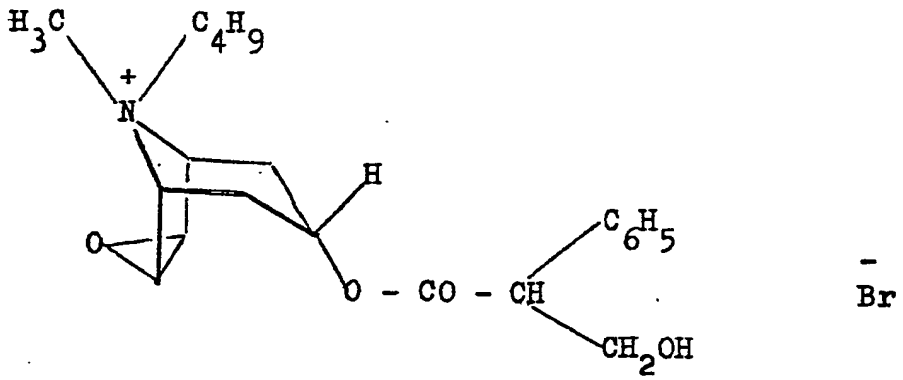
Atropine methylbromide and methylnitrate



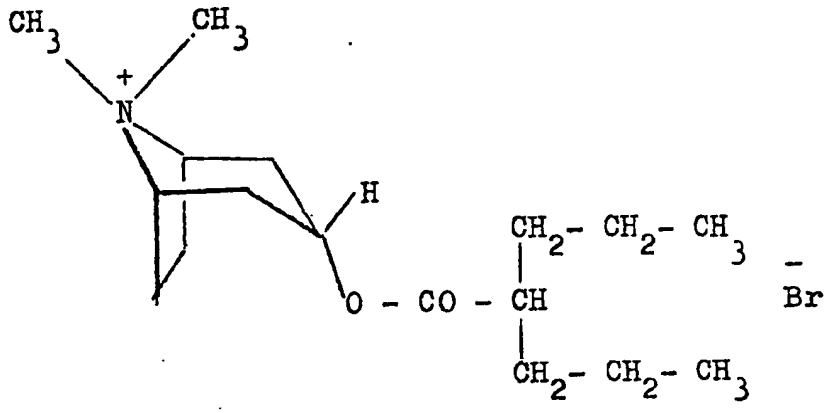
Methscopolamine bromide and nitrate



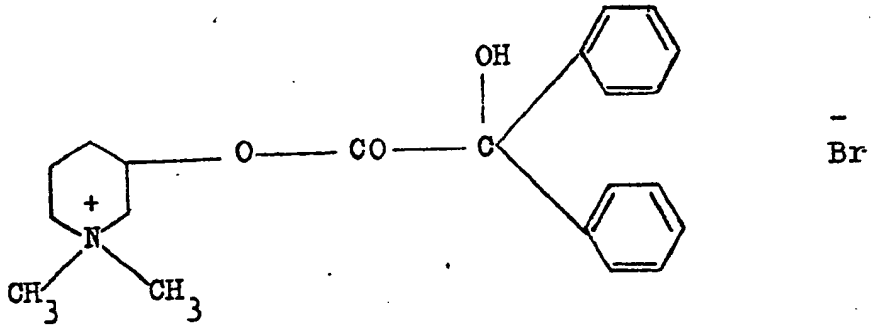
N-Buthyl scopolamine



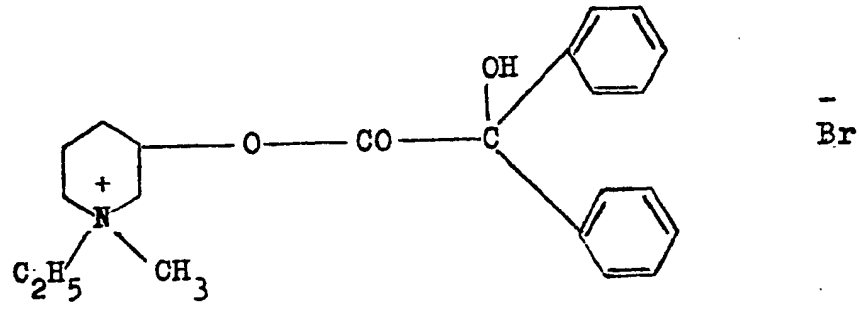
Anisotropine methylbromide



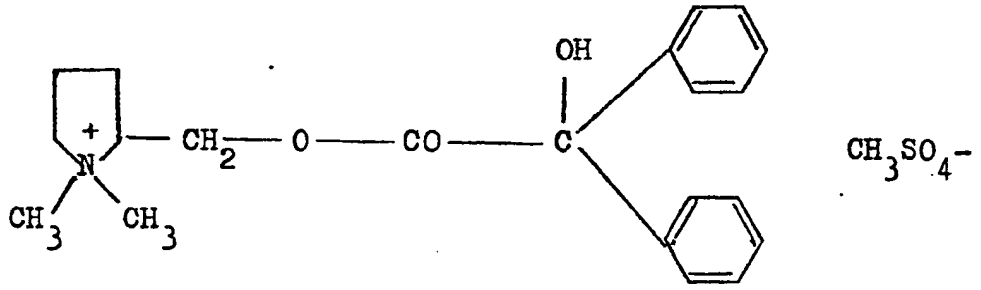
Mepenzolate bromide



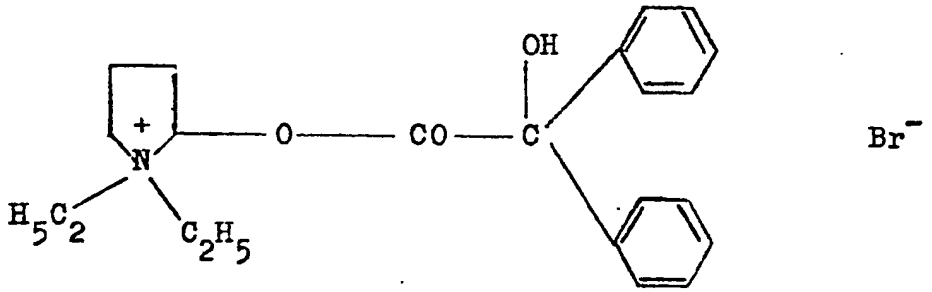
Pypenzolate bromide



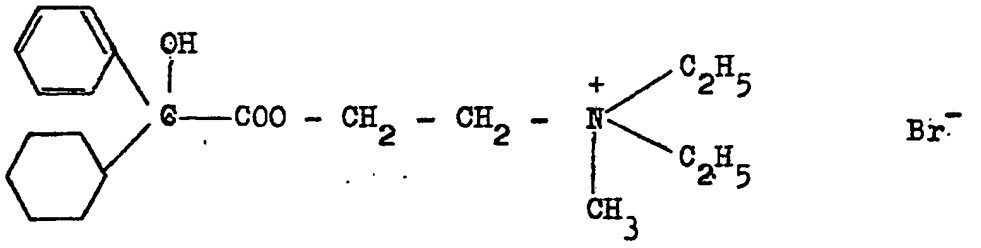
Poldine methylsulphate



Benzilonium bromide

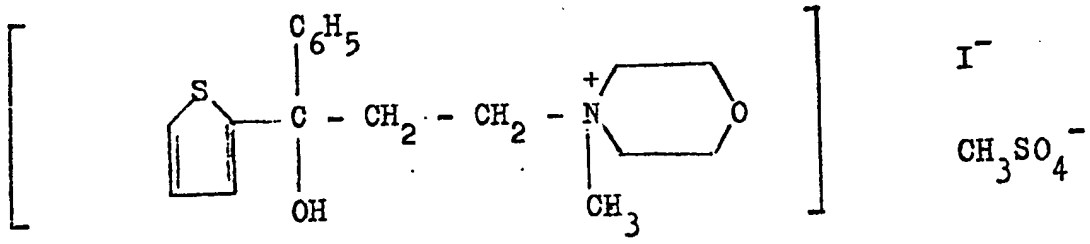


Oxyphenonium bromide

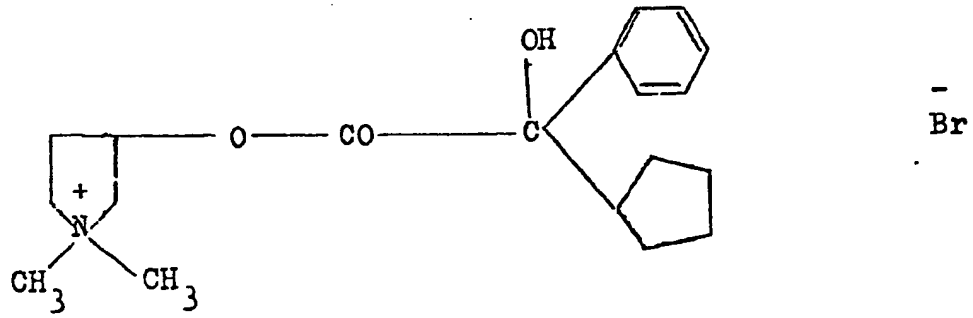


Other onium salts which are suitable to the purposes of the invention are:

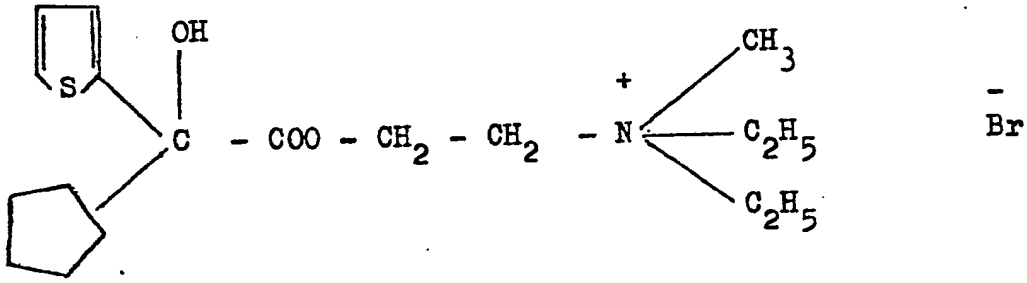
Thiemonium iodide and methylsulphate



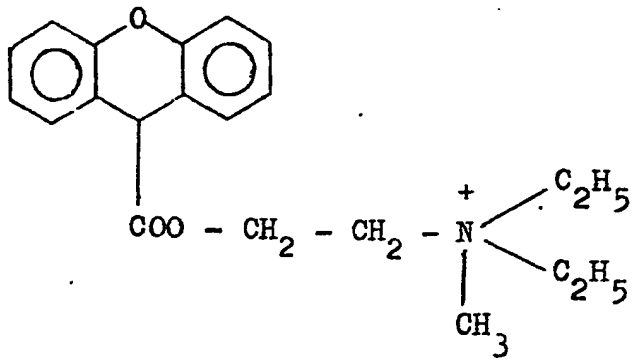
Glycopyrronium bromide



Penthienate bromide

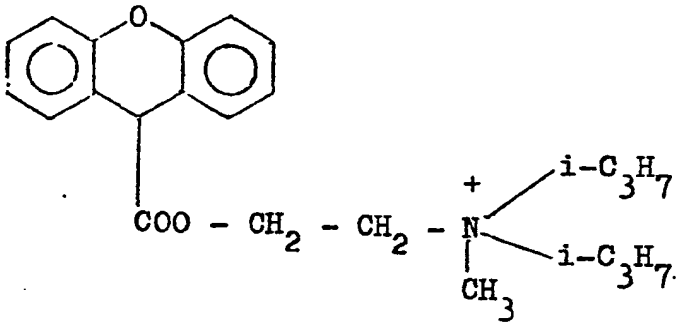


Methantheline bromide



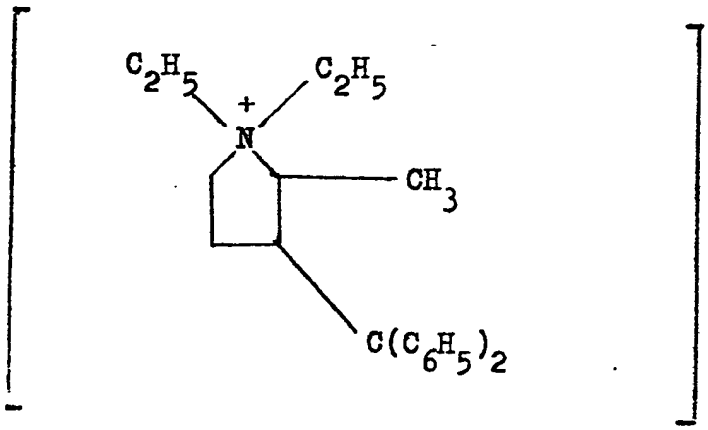
Br

Propantheline bromide



Br

Prifinium bromide



Br

According to the invention, the active compounds above defined are prepared as pharmaceutical compositions with a nasal carrier, which renders them suitable to be administered by intranasal way, with considerably better results than obtained by using the compositions intended for oral and rectal use, as far as an increased bioavailability of the active principle, and the minimization of the variations of the hematic levels of it are regarded, thus allowing these onium salts to be used at far lower dosage levels than usually employed for the use by oral and rectal way.

A surprising feature of the invention is that, very clearly, these onium salts are very rapidly absorbed from the nasal mucosa into the systemic hematic circulation, without first-pass metabolism. That is to say, an efficacious systemic anticholineesterasic and antimuscarinic therapeutical response is obtained.

Each one of the aforementioned onium salts can be conveniently administered by intranasal way to warm-blooded animals by means of formulations suitable for intranasal application, such formulations comprising the selected onium salt, in a suitable quantity to carry out the anticholineesterasic, agonist-cholinergic and antimuscarinic effect, together with a pharmaceutically acceptable and non-toxic nasal carrier.

The choice of the pharmaceutically acceptable and non-toxic carriers, which does not exclude the use of carriers traditionally mentioned in the art of nasal administering, depends on the chemical-physical characteristics of the onium salt, on the required dosages, on the selected type of formulation (solution, nasal gel,

nasal ointment, aerosol spray, and so on), on the stability of the onium salt, etc.

The preferred dosage forms by the intranasal way are almost always solutions, dispersions in water base, such base being either gelled or not; in any case, water may represent the main ingredient of the formulations.

Minor quantities are employed in the formulations, of other ingredients, such as buffering agents, wetting agents, dispersing agents, pH adjustment agents, gelling agents and viscosity increasers.

Compatibly with the nature and the complexity of the formulation, is it preferred that the formulation be isotonic.

It has been found additionally that the carriers with prevailingly aqueous base and at low viscosity, as well as those carriers which use propellants based on halogenated hydrocarbons, tend to increase the absorption rate.

As examples of halogenated hydrocarbons, trichlorofluoromethane, dichlorofluoromethane, trichlorotrifluoroethane and dichlorotetrafluoroethane are preferred.

The carriers based on gelled supports, on O/W and W/O emulsions, used for intranasal application or through nebulizing, allow effects to be obtained, which are more durable in time, without significantly penalizing the rapidity of such effects.

Should the onium salts be not stable enough in the ready-for-application formulations, the active principle can be freeze-dried on a suitable support (mannitol, glycine, etc), which will be dissolved and/or dispersed by the suitable vehicle at the moment of the intranasal ad

ministering only.

Examples of the preparation of typical nasal compositions containing onium salts pertaining to the class of parasympathetic-mimetic products are reported herein under. These Examples are reported for illustrative purposes only, and are not to be intended as limitative of the invention.

EXAMPLES

Example 1

Aqueous solution of Neostigmine methylsulphate for intranasal nebulizing (pH 6,4)

	% weight/volume	
Neostigmine methylsulphate	3	g
sodium chloride	0,9	g
Monopotassic phosphate	0,68	g
Sodium hydroxide	0,056	g
Methyl p-hydroxybenzoate	0,080	g
Propyl p-hydroxybenzoate	0,020	g
Glycerin	10	g
Depurated water, as much as necessary to	100	ml

The following products are dissolved in water, in the following order: neostigmine metylsulphate, sodium chloride, monopotassic phosphate, sodium hydroxide.

Methyl and propyl p-hydroxybenzoates are dissolved in glycerin, this solution is then added to the preceding one, carefully stirring.

The solution is administered by using nebulizers with pneumatic pump, and distributing valve rated at 50 - 100 microlitres per each nebulizing.

Example 2

Aqueous solution of thiemonium iodide for intranasal ne-

bulizing (pH 6,4)

	% weight/volume	
Thiemonium iodide	4	g
Sodium chloride	0,9	g
monopotassic phosphate	0,68	g
sodium hydroxide	0,056	g
methyl p-hydroxybenzoate	0,080	g
propyl p-hydroxybenzoate	0,020	g
glycerin	10	g
Propylene glycol	20	g
Depurated water, as much as necessary to	100	ml

The following products are dissolved in water, in the following order: thiemonium iodide; then sodium chloride, monopotassic phosphate, sodium hydroxide.

Methyl p-hydroxybenzoate and propyl p-hydroxy-benzoate are dissolved in glycerin and propylene glycol; when the solution is complete, it is added to the preceding one.

As for the therapeutical application, see Example 1.

Example 3

Aqueous solution of neostigmine methylsulphate, with increased viscosity, for intranasal nebulizing (pH 6,5)

	% weight/volume	
Neostigmine methylsulphate	3	g
sodium chloride	0,9	g
monobasic phosphate	0,680	g
sodium hydroxide	0,056	g
methyl p-hydroxybenzoate	0,080	g
propyl p-hydroxybenzoate	0,020	g
Hydroxypropylmethylcellulose	0,500	g

Depurated water, as much as necessary to 100 ml

Methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are dissolved in heated water; after cooling, neostigmine methylsulphate, sodium chloride, monopotassic phosphate, sodium hydroxide and hydroxypropylmethylcellulose are dissolved, in the order as shown.

Also this solution is preferably applied by means of nebulizers.

Example 4

Aqueous solution of thiemonium iodide, with increased viscosity, for intranasal nebulizing (pH 6,5)

	% weight/volume	
Thiemonium iodide	4	g
sodium chloride	0,9	g
monobasic phosphate	0,680	g
sodium hydroxide	0,056	g
methyl p-hydroxybenzoate	0,080	g
propyl p-hydroxybenzoate	0,020	g
hydroxypropylmethylcellulose	0,500	g
Glycerin	10	g
Propylene glycol	20	g
Depurated water, as much as necessary to	100	ml

Thiemonium iodide , then sodium chloride, monopotassic phosphate, sodium hydroxide, hydroxypropylmethylcellulose are dissolved in water, in the order shown.

Methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are dissolved in propylene glycol and glycerin; upon completion, this solution is added to the preceding one.

This formulation is applied as the solutions described in previous Examples 1, 2 and 3.

Example 5

Nasal gel of neostigmine methylsulphate (pH 7)

	% weight/volume	
Neostigmine methylsulphate	2,5	g
Carboxypolymethylene	1	g
propylene glycol	20	g
methyl p-hydroxybenzoate	0,08	g
propyl p-hydroxybenzoate	0,02	g
triethanolamine	1,1	g
depurated water, as much as necessary to	100	ml

In a share of water, neostigmine methylsulphate is added, and carboxypolymethylene is added.

Methyl p-hydroxybenzoate and propyl p-hydroxybenzoate are dissolved in propylene glycol; the thus obtained solution is added to the preceding one.

With the balance of water triethanolamine is dissolved; add this solution to the preceding one, mixing and stirring carefully.

The gel is applied as a normal ointment for nasal use.

Example 6

Nasal gel of thiemonium iodide (pH 7)

	% weight/volume	
Thiemonium iodide	3,5	g
Carboxypolymethylene	1,0	g
propylene glycol	20	g
methyl p-hydroxybenzoate	0,080	g
propyl p-hydroxybenzoate	0,020	g
triethanolamine	1,1	g
depurated water, as much as necessary to	100	ml

In a share of water thiemonium iodide is dissolv

ed, and carboxypolymethylene is then added.

Propylene glycol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate are completely dissolved; the so obtained solution is added to the preceding one.

With the balance of water, a solution is prepared of triethanolamine, such solution is carefully mixed and is then added to the other solution.

The gel is applied as a normal ointment for nasal use.

Example 7

Oily suspension of neostigmine methylsulphate for intranasal application (pH 6,3)

	% weight/volume	
Neostigmine methylsulphate	3	g
Triglycerids of vegetable fatty acids, as much as necessary to	100	ml

The particles of neostigmine methylsulphate shall have an average diameter of 10μ . pH 6,3.

The dispersion is carried out by any traditional method, such as colloid mill, and so on.

The dispersion is applied by nasal instillation, as the following Example too.

Example 8

Oily suspension of thiemonium iodide (pH 6,3)

	% weight/volume	
Thiemonium iodide	4	g
Triglycerids of vegetable fatty acids, as much as necessary to	100	ml

Particle diameter 10μ .

The suspension is prepared by dispersing the aotive principle in the oil, by any traditional system, such as

colloid mill for example.

Example 9

Freeze-dried composition of neostigmine methylsulphate (pH 5,6)

	% weight/volume	
Neostigmine methylsulphate	3	g
sodium chloride	0,9	g
mannitol	10	g
depurated water, as much as necessary to	100	ml

Mannitol, sodium chloride, neostigmine are dissolved in water.

The solution is distributed in vials, is chilled and is submitted to the freeze-drying procedure.

At the moment of use, the solution is restored, for intranasal nebulizing, by means of depurated water.

Example 10

Freeze-dried composition of thiemonium iodide (pH 5,6)

	% weight/volume	
Thiemonium iodide	4	g
sodium chloride	0,9	g
mannitol	10,0	g
depurated water, as much as necessary to	100	ml

Mannitol, sodium chloride and thiemonium iodide are dissolved in water.

The solution is distributed in vials, is chilled, and is submitted to the freeze-drying procedure.

At the moment of use, the solution is restored, by means of depurated water, which allow the intranasal nebulizing to be carried out.

Example 11

Salve for nasal application of neostigmine methyl-sul-

phate (pH 6,2)

	% weight/volume	
Neostigmine methylsulphate	3	g
carboxypolymethylene	1	g
triethanolamine	1,25	g
methyl p-hydroxybenzoate	0,08	g
propyl p-hydroxybenzoate	0,02	g
liquid paraffin	10,00	g
vaseline oil	10,00	g
castor oil P.O.E.	5,00	g
Depurated water as much as necessary to	100	g

In a share of the water, neostigmine methylsulphate is dissolved and then, under stirring, carboxypolymethylene.

The solution of triethanolamine in the balance of water is then added: the solution is thoroughly mixed and heated at 65°C.

A separated solution has been prepared by heating at 65°C liquid paraffin, vaseline oil and castor oil.

The oily solution is added to the aqueous one, and the stirring is continued, while slowly cooling down to room temperature.

The composition is applied as a normal ointment for nasal use.

Example 12

Nasal salve of thiemonium iodide (pH 6,2)

	% weight/volume	
Thiemonium iodide	4	g
carboxypolymethylene	1	g
triethanolamine	1,25	g
methyl p-hydroxybenzoate	0,080	g

propyl p-hydroxybenzoate	0,020	g
liquid paraffin	10,00	g
vaseline oil	10,00	g
castor oil P.O.E.	5,00	g
depurated water, as much as necessary to	100	g

In a share of the water the thiemonium iodide is dissolved, and, with stirring, the carboxypolymethylene; the solution is stirred until completion.

The solution of water/triethanolamine is then added. The total solution is heated at 65°C.

Liquid paraffin, vaseline oil and castor oil P.O.E. are heated at 65°C.

While being stirred, the aqueous and the oily solutions are combined.

Stirring is continued until the temperature has decreased down to room temperature.

This formulation is applied as a normal ointment for nasal use.

Example 13

Pressurized aerosol of neostigmine methylsulphate

	% weight/volume	
Neostigmine methylsulphate	3	g
soy lecithin	0,6	g
anhydrous ethanol	5	g
Frigen 113	20	g
Frigen 11/12/114	71,4	g

The neostigmine methylsulphate, previously pulverized to about 10 μ, is dispersed in anhydrous ethanol, soy lecithin and propellants are added, and the mixture is conditioned within aerosol bombs.

Example 14

Pressurized aerosol of thiemonium iodide

	% weight/volume	
Thiemonium iodide	4	g
soy lecithin	0,6	g
anhydrous ethanol	5	g
Frigen 113	20	g
Frigen 11/12/114	70,4	g

Thiemonium iodide is dispersed in ethanol, then soy lecithin, Frigen 113 and Frigen 11/12/114 are added, and the mixture is conditioned inside aerosol bombs.

Claims

1. Pharmaceutical composition with systemic anticholinesterasic activity, agonistic-cholinergic activity and antimuscarinic activity, characterized in that it contains a therapeutically active dose of a parasympathomimetic quaternary ammonium salt, and a nasal carrier suitable to be administered by nasal way.

2. Composition as claimed in claim 1, characterized in that said salt is selected among the following ones: edrophonium chloride, neostigmine bromide and methylsulphate, benzpyrinium bromide, pyridostigmine bromide, ambenonium chloride, atropine methylbromide and methylnitrate, methscopolamine bromide and nitrate, scopolamine butylbromide, anisotropine methylbromide, mepenzolate bromide, pypenzolate bromide, poldine methylsulphate, benzylonium bromide, oxyphenonium bromide, thiemonium iodide and methylsulphate, glycopyrronium bromide, penthienate bromide, methanteline bromide, propantheline bromide, prifinium bromide.

3. Composition as claimed in claim 1, characterized in that it is of isotonic character.

4. Composition as claimed in claim 1, characterized in that it is in the form of a nasal gel with prolonged release.

5. Composition as claimed in claim 1, characterized in that it is in the form of an ointment for nasal application, with prolonged release.

6. Composition as claimed in claim 1, characterized in that it is in the form of a propelled spray.

7. Composition as claimed in claim 1, characterized in that it is in the form of a freeze-dried product,

able to restore, at the time of use, a solution suitable to intranasal application.

0140434

CLAIMS FOR AUSTRIA

1. A process for preparing a composition with systemic anticholinesterasic activity, agonistic-cholinergic activity and antimuscarinic activity, characterized in mixing a therapeutically active dose of a parasympathomimetic quaternary ammonium salt, and a nasal carrier suitable to be administered by nasal way.

2. A process as claimed in claim 1, characterized in that said salt is selected among the following ones: edrophonium chloride, neostigmine bromide and methylsulphate, benzpyrinium bromide, pyridostigmine bromide, ambenonium chloride, atropine methylbromide and methylnitrate, methscopolamine bromide and nitrate, scopolamine butylbromide, anisotropine methylbromide, mepenzolate bromide, pypenzolate bromide, poldine methylsulphate, benzylonium bromide, oxyphenonium bromide, thiemonium iodide and methylsulphate, glycopyrronium bromide, penthienate bromide, methanteline bromide, propantheline bromide, prifinium bromide.

3. A process as claimed in claim 1, characterized in that said composition is of isotonic character.

4. A process as claimed in claim 1, characterized in that said composition is in the form of a nasal gel with prolonged release.

5. A process as claimed in claim 1, characterized in that said composition is in the form of an ointment for nasal application, with prolonged release.

6. A process as claimed in claim 1, characterized in that said composition is in the form of a propelled spray.

7. A process as claimed in claim 1, characterized in that said composition is in the form of a freeze-dried product, able to restore, at the time of use, a solution suitable to intranasal application.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☑ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.